REMARKS

Status of the Claims

With this response, Applicant has cancelled claims 9 and 10; amended claims 1, 3-5, and 8; and added new claim 13. Upon entry of this amendment, claims 1-8 and 11-13 will be pending—claims 1-6, 8, and 13 are under examination and claims 7, 11, and 12 are withdrawn. All claim amendments are made without prejudice.

Support for the amendments to the claims can be found throughout the application as filed, including original claims 1 and 11, and paragraphs [0014], [0031], [0032], and [0056]-[0058] of the published application, U.S. Patent Application Publication No. 2006/0199790. New claim 13 reads on the elected invention. Accordingly, these amendments do not add new matter and their entry is respectfully requested.

Rejections under 35 U.S.C. § 112 second paragraph

Claims 1-2, 4-6, and 8 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In particular, the Examiner alleges that the term "a drug" renders the claims indefinite.

The deletion of the term "a drug" from the claims and substitution of the term "composition" renders this rejection moot. Accordingly, this rejection may be withdrawn.

Rejection under 35 U.S.C. § 102

The cancellation of claim 9 renders its rejection moot.

Rejections under 35 U.S.C. § 103

I. *Chopp*

Claims 1-6, 8, and 10 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over U. S. Patent No. 6,245,757 to Chopp *et al.* (*Chopp*), as evidenced by Chemical Book, for the structure of pregnenolone methyl ether. The Examiner alleges that *Chopp* describes a method of treating ischemic damage comprising administering a progestin. Office Action at 6-7. The Examiner acknowledges that *Chopp* does not exemplify using pregnenolone methyl ether. *Id.* at 9. The Examiner, however, alleges that *Chopp* describes pregnenolone methyl ether as a useful progestin for the treatment, and would be motivated to use other progestins in the same method. *Id.* at 9-10.

II. *Stein*

Claims 1-6, 8 and 10 were also rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent Application Publication No. 2002/0072509 by Stein *et al.* (*Stein*), as evidenced by Chemical Book, for the structure of pregnenolone methyl ether. The Examiner alleges that Stein describes a method for treating neurodegeneration following a traumatic injury to the CNS (central nervous system) and that the neuro-protective effect is achieved by administering a composition comprising a progestin. Office Action at 11. The Examiner acknowledges that *Stein* does not exemplify using pregnenolone methyl ether in its Examples. *Id.* at 12. The Examiner, however, alleges that *Stein* suggests that pregnenolone methyl ether is a "useful progestin for protecting neuro-degeneration..." and that it would be obvious to use other disclosed progestins in the disclosed methods. *Id.* at 13.

III. Applicant's Response

Applicant respectfully traverses these two grounds for rejection. Obviousness rejections must be based on the claims as a whole, considering all claim features, and not merely the differences between the claims and cited references. *See* M.P.E.P. §§ 2141.02 (I), 2143.03. Furthermore, the courts have stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co. v. Teleflex Inc.*, 82 U.S.P.Q. 2d 1385, 1396 (2007), quoting *In re Kahn*, 78 U.S.P.Q. 2d 1329, 1336 (Fed. Cir. 2006); *see also* M.P.E.P. §§ 2141(II), 2142. Obviousness rejections further require a reasonable expectation of success when modifying or combining references. *See* M.P.E.P. § 2143.02(II).

Chopp and *Stein*, alone or in combination with the Chemical Book, do not render the instant claims obvious. Although both references recite pregnenolone methyl ether in a laundry list of compounds under the heading of "progestins," the skilled artisan would not have been motivated to use 3-methoxy-PREG or any other molecule according claim 1, in their methods, let alone with the necessary reasonable expectation of success, for the following reasons.

First, the skilled artisan would have recognized that *Chopp's* and *Stein's* classification of pregnenolone methyl ether as a progestin—*i.e.*, having progesterone activity—was incorrect. This is, in part, because 3-methoxy-PREG is modified to prevent it from being converted into progesterone (or its active metabolites) *in vivo.*

Secondly, the purported therapeutic effects of progestins reported in *Chopp* and

Stein were due to their progesterone activity. 3-methoxy-PREG, however, lacks this progesterone activity and even antagonizes it.

Finally, the purportedly therapeutic progestins used in *Chopp* and *Stein* lack the microtubule stabilizing activity required by Applicant's methods and as recited in Applicant's claims.

A. 3-methoxy-PREG is not a progestin

The Examiner's rejections appear to be based on the fact that *Chopp* and *Stein* both list pregnenolone methyl ether in a laundry list of alleged "progestins." The skilled artisan as of Applicant's 2003 priority date, however, would have recognized that this classification is completely erroneous. As discussed in the application, pregnenolone (PREG) is a ***precursor*** of all steroid hormones. Published application at [0009]. The conversion of PREG to active hormones begins with the conversion of the Δ5-3 β-OH of PREG to Δ4-3-keto. *Id.* 3-methoxy-PREG, however, is blocked at the Δ5-3 β-OH structure and therefore cannot be converted into metabolites with progestative, androgenic, estrogenic, or glucocorticoid activity. *Id.* at [0009]-[0010]. Accordingly, the skilled artisan would have recognized that 3-methoxy-PREG is not an active progestin molecule and is chemically blocked from being converted into an active progestin *in vivo*.

In addition, the attached Declaration under 37 C.F.R § 1.132 by inventor Etienne-Emile Baulieu (*Baulieu Declaration*), further illustrates that **1)** the skilled artisan as of Applicant's priority date would have understood that progestins are molecules with progesterone activity (*e.g.,* progesterone receptor agonists); and **2)** 3-methoxy-PREG lacks progesterone activity and even acts as a weak progesterone receptor ***antagonist.***

Furthermore, 3-methoxy-PREG does not significantly bind other steroid hormone receptors, even at doses as high as 10 μM. *See Baulieu Declaration* at paragraphs 10-13 and Exhibits E and F, confirming that 3-methoxy-PREG has neither progestative, androgenic, estrogenic, or glucocorticoid activity.

In particular, Exhibit F of the *Baulieu Declaration* includes experimental results—previously submitted to the Office (see Response filed July 22, 2008)—demonstrating that 3-methoxy-PREG does not activate a progesterone receptor reporter (Figure 1 of Exhibit F) and even acts as a weak progesterone receptor antagonist (Figure 2 of Exhibit F) in cell-based assays. See *Baulieu Declaration* at paragraphs 11-13. Accordingly, a skilled artisan would not have considered 3-methoxy-PREG a "progestin" and would not have been motivated to use it in the methods of *Chopp* and *Stein*, let alone with a *reasonable* expectation of success.

B. *Chopp* and *Stein* only describe using progesterone or downstream metabolites with GABA-receptor agonist activity

The Examiner acknowledges that *Chopp* and *Stein* fail to show any experimental results using 3-methoxy-PREG. In fact, the only progestins tested by *Chopp* and *Stein* were either progesterone or its downstream metabolites.

For example, *Stein* tested the effect of progesterone and two of its downstream metabolites, allopregnanolone and epipregnanolone, in a model of learning following traumatic brain injury. *Stein* at [0078]. Of the three progestins tested, only allopregnanolone elicited a statistically significant effect. *See Stein* at [0082] and Figure 2. Indeed, the claims in *Stein* are directed ***exclusively*** to methods of using allopregnanolone. Allopregnanolone is a known GABA receptor agonist. *See Stein* at [0006] and Exhibit D of the *Baulieu Declaration*.

Chopp, in turn, tested only one progestin—progesterone—in a model of ischemia. *See Chopp*, Examples. *Chopp* recognized that progesterone crosses the blood-brain barrier and gets converted into more active forms, such as 3α, 5α THP (allopregnanolone; *see, e.g.*, paragraph 8 and Exhibit D of the *Baulieu Declaration*). *Chopp* opines that progesterone's purported neuroprotective effect is due, at least in part, to its activity as a GABA receptor agonist. *See Chopp* at paragraph bridging columns 11 and 12. The skilled artisan would believe that this follows from its conversion to the more active allopregnanolone—a conclusion further supported by the results in *Stein*. Thus, as stated in paragraph 9 of the *Baulieu Declaration*, a person having ordinary skill in the art at the time of Applicant's invention would have believed that any neuroprotective effects of "progestins" suggested by *Chopp* and *Stein* would be mediated by progesterone or its metabolite allopregnanolone, acting as GABA receptor agonists.

In contrast, PREG—a precursor to progesterone—was known to be a GABA receptor ***antagonist***. *See* paragraph 10 and Exhibit E of the *Baulieu Declaration*. Since 3-methoxy-PREG is a blocked derivative of PREG, the skilled artisan would have also expected it to be a GABA receptor antagonist. Moreover, since 3-methoxy-PREG is blocked, it cannot be converted to progesterone or allopregnanolone *in vivo*, and would therefore retain its progesterone receptor and GABA receptor antagonist activity. *See, e.g.*, published application at [0009]-[0010].

Accordingly, since *Stein* and *Chopp* direct the skilled artisan to use progesterone or allopregnanolone, and since 3-methoxy-PREG is a non-metabolizable precursor to these molecules, which antagonizes their modes of action, the skilled artisan would be

further dissuaded from using 3-methoxy-PREG (or other molecules of formula I) to treat lesions or diseases of the nervous system.

C. Progesterone does not stabilize or stimulate polymerization of microtubules

Applicant's claims require, *inter alia*, administering "an amount [of a composition comprising 3-methoxy-PREG or its derivatives of formula I] effective to stimulate polymerization and/or stabilization of microtubules...." Applicant has demonstrated that 3-methoxy-PREG stimulates neurite outgrowth in cultures of PC12 cells by stimulating MAP2-dependent microtubule polymerization. *See* Examples 2 and 3; *see also* paragraph 14 of the *Baulieu Declaration*. Furthermore, Applicant has demonstrated that progesterone lacks this feature. *See* published application at [0079]; *see also Baulieu Declaration* at paragraph 14 and Figure 1b of Exhibit G. Accordingly, the skilled artisan would understand that progesterone and its downstream metabolites, such as allopregnanolone, are in no way interchangeable with 3-methoxy-PREG.

D. Conclusion

The Examiner's obviousness rejections should be withdrawn. Both rejections lack the explicit reasoning required by the courts. In both cases the Examiner merely states that the skilled artisan "would have had a reasonable expectation of success in producing the claimed invention." Office Action at 10, 13. The basis for this conclusion appears to be that both *Chopp* and *Stein* list pregnenolone methyl ether in a long list of alleged "progestins" and are therefore interchangeable with the progestins used in their studies. *Chopp* and *Stein*, however, offer no teaching or suggestion to specifically select any of the 3-methoxy-PREG-derivatives required by Applicant's claims from these laundry lists.

Additionally, the skilled artisan considering *Chopp* and *Stein* would recognize that 3-methoxy-PREG does not have progesterone activity and is chemically blocked from being converted to progesterone or its more active metabolites *in vivo.* As a result, the skilled artisan would dismiss it as a suitable substitute for the progestins used in *Chopp* and *Stein*. Moreover, Applicant has demonstrated that 3-methoxy-PREG actually *antagonizes* the modes of action of the progestins used in *Chopp* and *Stein*, while progesterone—the canonical progestin—fails to stimulate microtubule polymerization or stabilization, as required by Applicant's claims. Accordingly, the skilled artisan would not have been motivated or have a reasonable expectation of success in substituting 3-methoxy-PREG for the progestins used by *Chopp* and *Stein*—absent Applicant's disclosure. *See* M.P.E.P. § 2141.01(III) (avoiding impermissible hindsight).

Finally, even if the Examiner disagrees, Applicant has demonstrated that the molecules used in the claimed methods exhibit superior and unexpected properties, which rebut a *prima facie* obviousness rejection. *See* M.P.E.P. § 2145. For example, Applicant demonstrated that 3-methoxy-PREG dramatically increased neurite outgrowth (by up to 500%) in PC12 cells by stimulating microtubule polymerization. *See* published application at [0080], Figures 2-4; *see also* paragraphs 14-15 and Exhibit G of the *Baulieu Declaration*.

In conclusion, *Chopp* and *Stein*, alone or in combination with the Chemical Book, do not render Applicant's claims obvious. Accordingly, Applicant respectfully requests withdrawal of the rejection and reconsideration of the claims.

The Examiner is encouraged to call the undersigned with any questions. Please grant any extensions of time required to enter this Response and charge any additional required fees to our Deposit Account 06-0916.

Respectfully submitted,

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By: _____

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